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09/744875 C/C

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Doran R. Pace, Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. USF-T176X
Patent No. 7,002,003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Kenneth S. Zuckerman and Richard Y. Liu
Issued	:	February 21, 2006
Patent No.	:	7,002,003 B1
For	:	Method for the Inhibition of Function of STAT Transcription Factors

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate
APR 14 2006
of Correction

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Amendment dated September 3, 2003 reads:**
Column 3, line 27:	Page 4 of Amendment, lines 16 and 17:
"(SEQ 1D NO. 2 on"	--(SEQ ID NO. 2) on--

04/12/2006 CCHAU1 00000004 190065 7002003
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APR 18 2006

Patent Reads:	**Application Reads:**
Column 7, lines 31 and 32:	Page 13, lines 14 and 15:
"made to oligonucleotides is include"	--made to oligonucleotides include--
Column 9, line 41:	Page 17, line 20:
"and [P]-dATP"	--and [^{32}P]-dATP--
Column 9, line 51:	Page 17, line 30:
"10' horse serum"	--10% horse serum--
Column 10, line 35:	Page 19, lines 9 and 10:
"cells 1 x 10^6/mL were"	--cells (1 x 10^6/ml) were--
Column 10, line 40:	Page 19, lines 14 and 15:
"published is protocol"	--published protocol--
Column 10, lines 51 and 52:	Page 19, line 25:
"by 7.5 k"	--by 7.5%--
Patent Reads:	**Supplemental Amendment dated September 8, 2003 Reads:**
Column 11, line 5:	Page 2 of Amendment, line 24:
"(YL 1993"	--(Yu 1993--
Column 11, line 32:	Page 3 of Amendment, line 12:
"and 4455 mM"	--and 44.5 mM--
Patent Reads:	**Application Reads:**
Column 12, lines 11 and 12:	Page 22, lines 14 and 15:
"final is four"	--final four--

APR 18 2006

Column 12, line 14:	Page 22, line 17:
"stimulation of [3H]"	--stimulation of [^{3}H]-TdR--
Patent Reads:	**Supplemental Amendment dated September 8, 2003 Reads:**
Column 12, line 66:	Page 4 of Amendment, line 8:
"ISRE SEQ ID NO. 8"	--ISRE (SEQ ID NO. 8)--
Column 12, lines 67:	Page 4 of Amendment, line 9:
"inhibition or the"	--inhibition of the--
Column 13, line 8:	Page 4 of Amendment, line 14:
"{^{32}P}- labeled"	--[^{32}P]-labeled--
Column 13, line 13:	Page 4 of Amendment, line 18:
"constitutive"	--constitutively--
Column 13, line 18:	Page 4 of Amendment, line 20:
"in labeled"	--unlabeled--
Patent Reads:	**Application Reads:**
Column 14, lines 52 and 53:	Page 27, lines 14 and 15:
"constitutive is activation"	--constitutive activation--
Patent Reads:	**Amendment dated October 29, 2004 Reads:**
Column 22, line 13:	Page 5 of Amendment, Claim 37, lines 1 and 2:
"wherein said tide"	--wherein said oligonucleotide--
Column 22, line 17:	Page 5 of Amendment, Claim 38, lines 1 and 2:
"wherein said tide"	--wherein said oligonucleotide--

APR 18 2006

Column 22, lines 24 and 25:	Page 8 of Amendment, Claim 65, line 1:
"oligonucleotide the"	--oligonucleotide consists of the--

A true and correct copy of pages 13, 17, 19, 22, and 27 of the specification as filed, as well as copies of Amendments dated September 3, 2003, September 8, 2003, and October 29, 2004, which support Applicants' assertion of the errors on the part of the Patent Office, accompany this Certificate of Correction.

The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065. Two copies of this letter are enclosed for Deposit Account authorization.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRP/lkw

Attachments: Copy of pages 13, 17, 19, 22, and 27 of the specification as filed; copies of Amendments dated September 3, 2003, September 8, 2003, and October 29, 2004.

APR 18 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,002,003 B1

APPLICATION NO.: 09/744,875

DATED : February 21, 2006

INVENTOR : Kenneth S. Zuckerman, Richard Y. Liu

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

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Line 27, "(SEQ 1D NO. 2 on" should read --(SEQ ID NO. 2) on--.

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Column 10,
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Column 11,
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Column 13,
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Column 13,
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In addition, analogues of nucleotides can be prepared wherein the structure of the nucleotide is fundamentally altered and that are better suited as therapeutic or experimental reagents. An example of a nucleotide analogue is a peptide nucleic acid (PNA) wherein the deoxyribose (or ribose) phosphate backbone in DNA (or RNA) is replaced with a polyamide backbone which is similar to that found in peptides. PNA analogues have been shown to be resistant to degradation by enzymes and to have extended lives *in vivo* and *in vitro*. Further, PNAs have been shown to bind stronger to a complementary DNA sequence than a DNA molecule. This observation is attributed to the lack of charge repulsion between the PNA strand and the DNA strand. Other modifications that can be made to oligonucleotides include polymer backbones, morpholino polymer backbones [U.S. Patent 5,034,506], cyclic backbones, or acyclic backbones, sugar mimetics or any other modification including which can improve the pharmacodynamics properties of the oligonucleotide.

The oligonucleotides and ribozymes of the present invention can be synthesized by any method known in the art for ribonucleic or deoxyribonucleic nucleotides. For example, the oligonucleotides can be prepared using solid-phase synthesis such as in an Applied Biosystems 380B DNA synthesizer. Final purity of the oligonucleotides is determined as is known in the art.

Delivery of therapeutics (compound):

The therapeutic compound of the present invention is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, patient age, sex, body weight and other factors known to medical practitioners. The pharmaceutically "effective amount" for purposes herein is

EXAMPLE 1

Reagents

Recombinant human thrombopoietin (TPO), interleukin (IL)-3, IL-6, and granulocyte macrophage colony-stimulating factor (GM-CSF) were purchased from PeproTech (Rocky Hill, NJ). Anti-IL-3 and anti-TPO neutralizing antibodies were purchased from R & D system (Minneapolis, MN). Anti-phosphotyrosine antibody-agarose and anti-JAK2 antiserum were purchased from Upstate Biotechnology (Lake Placid, NY). Phosphotyrosine western blotting kit (chemiluminescence) was purchased from Boehringer Mannheim Biochemicals (Indianapolis, IN). Anti-goat IgG and anti-mouse IgG antibodies labeled with fluorescein isothiocyanate were purchased from Zymed (South San Francisco, CA). Anti-STAT1, -STAT2, -STAT3, -STAT4, -STAT5 and -STAT6 antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). [Methyl-^{3}H]-thymidine ([^{3}H]-TdR; Specific activity 70-86 Ci/mmol) and [^{32}P]-dATP (specific activity >3000 μCi/mmol) were purchased from Amersham Life Science (Arlington Heights, Illinois).

Cell lines

Human megakaryocytic leukemic cell line, HEL/Dami, originally described by Greenberg et al (1988 Blood 72:1968), was obtained from American Type Culture Collection (ATCC) and was maintained in Iscove's Modified Dulbecco's Medium (IMDM; GIBCO-BRL, Grand Island, NY) containing 10% horse serum or sera-free nutridoma HEL. Recently, ATCC and DSMZ (German Collection of Microorganisms and Cell Cultures) have determined that all samples of the HEL/Dami cell line that were available for them to analyze were genetically and karyotypically

were cultured for 72 hours without or with cytokines. Subsequently, the cells were labeled with 2 μCi/ml of [^{3}H]-TdR for an additional 4 hours. Incorporation of [^{3}H]-TdR into newly synthesized DNA (counts per minute; CPM) was determined by liquid scintillation counting, according to a previously described protocol (Lui 1992 Cancer Res, 52:3667). For the analysis of cell ploidy, cytokine-starved Mo7e cells (1x10^6 cells/ml) were cultured in IMDM medium with 10% FBS plus growth factors. Dami/HEL and Meg-01 cells (1x10^6/ml) were cultured in medium with 1x Nutridoma-HU plus growth factors, at 37°C for 1 to 10 days. The treated cells were harvested on day 3, 5, 7 and 10. The DNA content of the cells was quantitated with a FACScan flow cytometer (Becton Dickson, Rutherford, NJ), following a published protocol (Taylor 1980 J Histochem Cytochem 28:1021. Isolated human lymphocytes were used as a diploid control.

Immunoprecipitation and Western blotting

Unstimulated or cytokine-stimulated cells were lysed in modified RAPI buffer with 1% NP-40, and extracts were immunoprecipitated, as described (Dusanter-Fourt 1994). The detergent-soluble proteins were incubated with anti-phosphotyrosine agarose for 3 hours at 4°C with shaking. The immunoprecipitates were washed four times with modified RAPI buffer, lysed in SDS buffer and separated by 7.5% non-reducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Proteins then were transferred to nitrocellulose membrane and probed sequentially with rabbit anti-JAK2 antibody and anti-rabbit IgG antibody labeled with peroxidase. Phosphorylated JAK2 was visualized with enhanced chemiluminescence techniques according to the manufacturer's recommended procedure. For the detection of tyrosine phosphorylation of MAPK and other cellular proteins, cells treated with or without cytokines were lysed in SDS buffer, and 30 μg of protein was loaded

section. If Mo7e-stimulating activity is detected in the medium, it would imply that the factor-independent cell lines may produce and secrete autocrine stimulatory factor(s). If no Mo7e proliferation-stimulating activity of the conditioned medium is detected, the involvement of humoral factors in the factor-independent growth of Dami/HEL and Meg-01 cells is reduced substantially.

Human Megakaryocytic leukemic cell lines Dami/HEL and Meg-01 cells grow in a factor-independent manner

To determine effects of cytokines on DNA synthesis of the proliferating cells, various concentrations of cytokines were incubated with Dami/HEL, Meg-01, and Mo7e cells for 3 days and labeled subsequently with [^{3}H]-TdR for the final four hours of culture. When 0-200 ng/ml of TPO was incubated with the cytokine-independent cell lines, Dami/HEL and Meg-01, no significant stimulation of [^{3}H]-TdR incorporation was observed. The cells also were tested for their response to other cytokines, including GM-CSF, IL-3, IL-6 and TNF-α, and neither Dami/HEL nor Meg-01 cell proliferation is affected by any of these cytokines. Addition of anti-IL-3 or anti-TPO neutralizing antibodies did not inhibit [^{3}H]-TdR incorporation or cell proliferation. However, when factor-dependent Mo7e cells were incubated with various concentration of TPO, incorporation of [^{3}H]-TdR was stimulated significantly, in a dose-dependent manner. At the concentration of 50 ng/ml, TPO regularly stimulates the incorporation of [^{3}H]-thymidine 4.5-fold over that of control Mo7e cells at 3 days. IL-3, GM-CSF, IL-6, and TNF-α also stimulated Mo7e cell proliferation.

To investigate effects of cytokines on the maturation of these megakaryocytic leukemic cell lines, the cells were stained with propidium iodide, and cell ploidy was analyzed

resulted in death of the leukemic cells.

EXAMPLE 2

STAT5 Activation Is Essential for Growth Factor-Independent survival and proliferation of HEL/Dami and Meg-01 Cell Lines:

AG490 (but not PD098059) blocked the constitutive activation of STAT5 in HEL/Dami and Meg-01 cells, but it had no effect on growth factor-induced MAPK pathway activation. Moreover, AG490 (but not PD098059) inhibited the factor-independent proliferation of HEL/Dami and Meg-01 cells in a dose-dependent manner. The constitutive activation of JAK2 and STAT5 in HEL/Dami and Meg-01 cells, the inhibition of HEL/Dami and Meg-01 cell proliferation by AG490, and the lack of constitutive activation of the MAPK pathway in these cell lines show that the JAK2/STAT5 pathway is essential for the factor-independent growth of HEL/Dami and Meg-01 cells. By using dominant-negative (DN) STAT5 transfections the effect on factor-independent proliferation of these cell lines that express constitutively activated JAK2 and STAT5 was assessed. In order to regulate time and degree of DN-STAT5 expression, the Invitrogen ecdysone-inducible expression vector system was used. This involves double stable transfections with one vector (pVgRXR) containing the ecdysone receptor cDNA and a second vector (pIND) containing the construct of interest(e.g.,DN-STAT5 cDNA) driven by an ecdysone/muristerone/ponasterone-inducible promoter, with selection in zeocin and G418. HEL/Dami, Meg-01, and Mo7e cells stably transfected with the ecdysone receptor, and HEL/Dami cells that also contain the inducible DN-STAT5 construct in pIND were made. There was a significant

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Doran R. Pace, Patent Attorney

AMENDMENT UNDER 37 CFR §1.111
Examining Group 1635
Patent Application
Docket No. USF-T176X
Serial No. 09/744,875

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Mary M. Schmidt
Art Unit	:	1635
Applicants	:	Kenneth S. Zuckerman, Richard Y. Liu
Serial No.	:	09/744,875
Filed	:	January 29, 2001
Conf. No.	:	8728
For	:	Method for the Inhibition of Function of STAT Transcription Factors

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 CFR §1.111

Sir:

A Petition and Fee for a three-month Extension of Time through and including September 3, 2003, accompanies this Amendment.

In response to the Office Action dated March 3, 2003, please amend the above-identified patent application as follows:

In the Specification

Please substitute the following Title of the invention on page 1, lines 5-6:

METHOD FOR THE [MODULATION] INHIBITION OF
FUNCTION OF STAT TRANSCRIPTION FACTORS

Please substitute the following paragraph beginning on page 1, line 11:

[This work was supported in part by grants from the US Public Health Service, the National Institutes of Health and the National Cancer Institute] This invention was made with government support under National Institutes of Health grant number NCI 5 RO1 CA56072. The government has certain rights in the invention.

Please substitute the following Cross-Reference to Related Applications paragraph, on page 1, after the Title:

[This patent application is a National Phase Concerning a Filing Under 35 U.S.C. 371, claiming the benefit of priority of PCT/US99/17366, filed July 30, 1999, which claims the benefit of priority of U.S. Provisional Application Serial No. 60/094,695, all of which are incorporated herein by reference] This application is a U.S. national stage application of international patent application No. PCT/US99/17366, filed July 30, 1999, which claims the benefit of U.S. Provisional Application Serial No. 60/094,695, filed July 30, 1998.

Please substitute the following paragraph beginning at page 2, line 25, through to page 3, line 1:

A third method involves dominant-negative mutant transfections. This includes the transfection of cDNA encoding non-functional mutants of specific transcription factors or proteins that interact with the transcription factors[,]. [such] Such mutants are non-functional, and also interfere with the function of the normal endogenous transcription factor within the cells. These have the disadvantage of the technical difficulty of performing the transfections, isolating the cells that actually are expressing the dominant-negative protein, and regulating the level of expression of the dominant-negative protein in the cells.

Please substitute the following paragraph beginning at page 3, line 8:

There is provided a method of modulating the function of a transcription factor by administering an effective amount of an oligonucleotide containing optimal nucleotide binding sites for the transcription factor. A therapeutic agent having an effective amount of an oligonucleotide for modulating function of transcription factors and a pharmaceutically acceptable carrier is also provided. There is provided [~~an~~] oligonucleotides having transcription factor modulatory properties. Also provided is a treatment of patients having illnesses in which the activation of transcription factors play a role, by administering to a patient an effective amount of an oligonucleotide which competitively binds the related transcription factor. Also provided is a method of determining prognostic factors associated with particularly malignant cells by determining if particular transcription factors are constitutively activated.

Please substitute the following paragraphs beginning at page 3, line 32, through to page 5, line 24:

Figure 1 shows the sequence of the sense strand of double-stranded DNA fragments that were used for gel mobility assays and for the inhibition of the activation of STAT5;

Figure 2 shows the constitutive activation of a STAT-like DNA-binding factor in Dami/HEL and Meg-01 cells; Nuclear extracts from each cell line cultured in the absence of cytokine (CTL) or in the presence of as much as 400 ng/ml TPO or 40 ng/ml IL-3, were incubated with [^{32}P]-labeled, double-stranded IRF-1 GAS (SEQ ID NO. 2) oligonucleotide; The DNA-binding complex and unbound probes were separated electrophoretically on 5% non-denaturing polyacrylamide gels; The autoradiograph shows the STAT-like DNA-binding factor (DBF) and the nonspecific bands (NSB);

Figure 3 shows the identification of the constitutively activated DNA-binding factor in HEL/Dami and Meg-01 cells by gel electrophoretic mobility supershift assays; Nuclear extracts from HEL/Dami and Meg-01 cells without cytokine exposure were incubated with the [^{32}P]-labeled MGFe probe (SEQ ID NO. 1) plus anti-STAT3 antiserum (S3), or with the [^{32}P]-labeled probe plus anti-STAT5 antiserum (S5); The autoradiograph shows the STAT DNA-binding factor (DBF), nonspecific bands (NSB) and free IRF-1 GAS probe (P) (SEQ ID NO. 2); The arrowheads indicate the supershifted complexes, these results are representative of three separate experiments; Nuclear

extracts also were incubated with the [^{32}P]-labeled MGFe probe (SEQ ID NO. 1) plus anti-STAT1, anti-STAT2 and anti-STAT6 antiserum, no supershifted complexes were observed;

Figure 4 shows the effects of IRF-1 GAS (SEQ ID NO. 2) on the binding of STAT 5 to the [^{32}P]-labeled MGFe (SEQ ID NO. 1); Nuclear extracts from HEL/Dami and Meg-01 cells were incubated with the [^{32}P]-labeled MGFe probe (SEQ ID NO. 1) without IRF-1 GAS (NONE) (SEQ ID NO. 2) or with [^{32}P]-labeled probe plus a 100-fold excess of unlabeled oligonucleotide SIE (SEQ ID NO. 9) or IRF-1 GAS (I-GAS) (SEQ ID NO. 2), respectively; The DNA binding ~~compleses~~ complexes were separated in a 5% non-denaturing polyacrylamide gel; The autoradiograph shows the STAT transcription factor (STAT5) and nonspecific bands (NSB);

Figure 5 shows the effects of IRF-1 GAS double-stranded oligonucleotide (SEQ ID NO. 2) on HEL/Dami and Meg-01 cell survival and proliferation; HEL/Dami and Meg-01 cells were incubated with the ~~indicatied~~ indicated concentrations of IRF-1 GAS oligo (SEQ ID NO. 2) or SIE control oligo (SEQ ID NO. 9) with lipid for 72 hours and labeled with 2μ Ci/ml [^{3}H]-thymidine (TdR); TdR incorporation into newly synthesized DNA was determined by counting the radioactivity (CPM) from triplicate samples and expressed as the mean CPM; and

Figure 6 shows the effects of IRF-1 GAS double-stranded oligonucleotide (SEQ ID NO. 2) on HEL/Dami cell survival and proliferation; HEL/Dami cells were incubated with the indicated concentrations on STAT1 (SEQ ID NO. 10), STAT3 (SEQ ID NO. 11), MGFe (SEQ ID NO. 1), STAT5/6 (SEQ ID NO. 3) oligo or no oligo control (CTL) with lipid for 72 hours and labeled with 2μ Ci/ml [^{3}H]-thymidine (TdR); TdR incorporation into newly synthesized DNA was determined by counting the radioactivity per minute (CPM) from triplicate samples and expressed as the mean CPM.

Please replace original pages 1-3 (Sequence Listing) with new pages 1-3 attached hereto.

In the Claims

1 (currently amended). A method [of modulating] for inhibiting the function of a transcription [factors by] factor, said method comprising administering an effective amount of [an] a double-stranded oligonucleotide [containing optimal nucleotide binding sites for the transcription factor], said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, and wherein said transcription factor binds to said oligonucleotide.

Claims 2-7 (canceled)

8 (currently amended). A [pharmaceutical] composition for inhibiting a transcription factor in a cell comprising [an effective amount of] a [double stranded] double-stranded oligonucleotide, said oligonucleotide having [a sequence bound by a transcription factor] a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, and wherein said transcription factor binds to said oligonucleotide.

9 (currently amended). The [pharmaceutical] composition according to claim [9] 8, wherein [in which] said transcription factor is activated.

10 (currently amended). The [pharmaceutical] composition according to claim 9, wherein said transcription factor is constitutively activated.

11 (currently amended). The [pharmaceutical] composition according to claim [9] 8, wherein the cell is a malignant cell.

12 (currently amended). The [pharmaceutical] composition according to claim [9] 8, wherein the cell is a leukemia cell.

13 (currently amended). The [pharmaceutical] composition according to claim 8, wherein said transcription factor is STAT5 [and said oligonucleotide contains the sequence TTCNNNGAA, in which "N" is any nucleotide].

Claim 14 (canceled)

15 (currently amended). The [pharmaceutical] composition according to claim 13, wherein said oligonucleotide [is selected from the group comprising an oligonucleotides having] comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1)[, GCCTGATTTCCCCGAAATGACGGCA (SEQ ID NO:2) and GTATTTCCCAGAAAAGGAAC (SEQ ID NO:3)].

16 (currently amended). A method of inhibiting [malignant] proliferation of a tumor cell by administering an effective amount of a [double stranded] double-stranded oligonucleotide, [the] said oligonucleotide having [a sequence bound by a transcription factor,] a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, and wherein a transcription factor in said tumor cell binds to said oligonucleotide, the transcription factor activity being correlated to [malignant] proliferation of said tumor cell.

Claims 17-18 (canceled)

19 (currently amended). A method of removing [malignant] a tumor cell in vitro by exposing a cell culture to an effective amount of a double-stranded oligonucleotide [containing optimal nucleotide binding sites for a transcription factor], said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, and wherein a transcription factor in said tumor cell binds to said oligonucleotide, the transcription factor activity being correlated to proliferation of said tumor cell.

20 (currently amended). [A therapeutic] An agent comprising an effective amount of [an] a double-stranded oligonucleotide [for modulating the function of transcription factors] of claim 8 and a pharmaceutically effective carrier.

21 (new). The agent according to claim 20, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).

22 (new). The agent according to claim 20, wherein said transcription factor is STAT5.

23 (new). The agent according to claim 20, wherein said transcription factor is activated.

24 (new). The agent according to claim 23, wherein said transcription factor is constitutively activated.

25 (new). The agent according to claim 20, wherein said cell is a malignant cell.

26 (new). The agent according to claim 20, wherein said cell is a leukemia cell.

27 (new). The agent according to claim 20, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

28 (new). The agent according to claim 20, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

29 (new). The agent according to claim 20, wherein said cell is a human cell.

30 (new). The method according to claim 1, wherein said transcription factor is STAT5.

31 (new). The method according to claim 1, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).

32 (new). The method according to claim 1, wherein said transcription factor is activated.

33 (new). The method according to claim 32, wherein said transcription factor is constitutively activated.

34 (new). The method according to claim 1, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

35 (new). The method according to claim 1, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

36 (new). The composition according to claim 8, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).

37 (new). The composition according to claim 8, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

38 (new). The composition according to claim 8, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

39 (new). The composition according to claim 8, wherein said cell is a human cell.

40 (new). The method according to claim 16, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).

41 (new). The method according to claim 16, wherein said transcription factor is STAT5.

42 (new). The method according to claim 16, wherein said transcription factor is activated.

43 (new). The method according to claim 42, wherein said transcription factor is constitutively activated.

44 (new). The method according to claim 16, wherein said cell is a malignant cell.

45 (new). The method according to claim 16, wherein said cell is a leukemia cell.

46 (new). The method according to claim 16, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

47 (new). The method according to claim 16, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

48 (new). The method according to claim 16, wherein said cell is a human cell.

49 (new). The method according to claim 19, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).

50 (new). The method according to claim 19, wherein said transcription factor is STAT5.

51 (new). The method according to claim 19, wherein said transcription factor is activated.

52 (new). The method according to claim 51, wherein said transcription factor is constitutively activated.

53 (new). The method according to claim 19, wherein said cell is a malignant cell.

54 (new). The method according to claim 19, wherein said cell is a leukemia cell.

55 (new). The method according to claim 19, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

56 (new). The method according to claim 19, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

57 (new). The method according to claim 19, wherein said cell is a human cell.

Remarks

Claims 1-3, 6-13, 15-17, 19, and 20 are pending in the subject application. Applicants acknowledge that claims 4, 14, and 18 have been withdrawn from further consideration as being drawn to a non-elected invention. Applicants also gratefully acknowledge the Examiner's indication that claims 6, 16, 17, 19, and 20 are free of the prior art. By this Amendment, Applicants have canceled claims 2-7, 14, 17, and 18, amended claims 1, 8-13, 15, 16, 19, and 20, and added new claims 21-57. Support for the amendments and new claims can be found throughout the subject specification including, for example, at page 28, lines 29-32, and in the claims as originally filed. Applicants have also amended the "Cross-Reference to Related Applications" section of the subject specification to update the cross-reference to prior applications and have amended the subject specification to include a "government support" paragraph. In addition, Applicants have amended the title of the invention to correspond to amendments made to the claims. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1, 8-13, 15, 16, and 19-57 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants note that a replacement sequence listing is being submitted in computer readable format and on paper with this Amendment. The replacement sequence listing includes sequences of the STAT1 and STAT3 binding sequences shown in Figure 1 of the subject specification that had not been provided in the prior sequence listing. The specification has been amended to include reference to appropriate SEQ ID numbers. I hereby certify that the paper and computer readable copies contain the same information and that no new material is added by this submission. Entry and consideration of the sequence listing is respectfully requested.

The specification is objected to on the grounds that it fails to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, the Examiner indicates that nucleic acid sequences are shown on pages 3-5 of the subject specification without including their corresponding SEQ ID numbers. By this Amendment, Applicants have amended the subject specification to include the SEQ ID NO. for the sequences shown at pages 3-5 of the specification. The specification is also objected to for a grammatical/typographical error on page 3, line 15. Applicants have amended page 3 of the subject specification to correct the inadvertent typographical error contained therein.

Applicants have also amended the subject specification to correct other miscellaneous typographical errors therein. Accordingly, reconsideration and withdrawal of the objections to the specification is respectfully requested.

The Examiner states that the Information Disclosure Statement (IDS) "filed 08/31/01 fails to comply with 37 CFR. 1.98(a)(2)." Specifically, the Examiner indicates that the references B, E, G-J, L, N, P, Q, Y, Z, and AA were not considered because a copy of the references was not provided with the IDS. Applicants are submitting herewith a Supplemental IDS with copies of references which were not available at the time the August 28, 2001 IDS was filed. Applicants respectfully request that the references cited in the Supplemental IDS be considered and made of record by the Examiner in the subject application.

Claims 3, 15, and 17 are objected to because of grammatical and typographical errors. Applicants have amended or canceled the claims, thereby rendering this objection moot. Reconsideration and withdrawal of the objection is respectfully requested.

Claims 9-12 are rejected under 35 USC §112, second paragraph, as indefinite. Applicants have amended claim 9 to correct the dependency such that claim 9 depends from claim 8. Applicants gratefully acknowledge the Examiner's careful review of the claims. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 1-3, 6-8, 13, 15-17, and 20 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. In addition, claims 1-3, 6-13, and 15-20 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully assert that the claims are enabled by the subject specification and that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention.

The Examiner does acknowledge under the rejection that the subject specification enables methods for inhibiting the function of a transcription factor in cell culture using the oligonucleotides of the invention. However, the Examiner asserts under the rejection that the subject specification does not enable *in vivo* treatment of whole organisms and that factors for the delivery of double

stranded transcription factor decoy (TFD) oligonucleotides parallel the unpredictabilities found in the art associated with antisense technology. In particular, the Examiner asserts that "there is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications." Applicants respectfully assert that the use of double-stranded TFD oligonucleotides of the invention does not parallel those factors and barriers noted by the Examiner associated with antisense oligonucleotides. For example, Applicants respectfully assert that the oligonucleotides of the present invention can be successfully delivered to target cells, both *in vitro* and *in vivo*. Furthermore, antisense oligonucleotides, as the Examiner correctly points out, must hybridize in a sequence-specific manner with a target nucleic acid, whereas in the case of double-stranded TFD oligonucleotides of the invention, the transcription factors readily recognize the binding sequence presence on the TFD oligonucleotides. The Examiner also states in the Office Action that the "Discovery of antisense molecules with 'enhanced specificity' *in vivo* requires further experimentation for which no guidance is taught in the specification." The Examiner also quotes the Branch reference: "it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Applicants point out, however, that the oligonucleotides of the invention are not "antisense molecules." Thus, issues of antisense technology, *i.e.*, what portions of an RNA molecule will be accessible, *etc.* are not relevant to the oligonucleotides of the invention because they do not rely on nucleic acid hybridization but rather involve nucleic acid:protein binding. Thus, Applicants respectfully assert that the teachings in the Ma *et al.*, Jen *et al.*, Green *et al.*, Agrawal *et al.*, Branch and Bennett publications concerning antisense oligonucleotides are not directly applicable to the technology of the subject application and that oligonucleotides of the invention can be delivered and used to treat whole organisms *in vivo*.

However, by this Amendment, Applicants have amended the claims to delete references to "pharmaceutical" and "therapeutic" from the preamble of the claims, which the Examiner has indicated would overcome the rejection of the composition and agent claims. The methods of independent claims 1, 16, and 19 can be practiced *in vitro*. Applicants respectfully assert, however, that the claimed invention can be used in therapeutic and pharmaceutical applications. Applicants have also amended the independent claims to recite that the oligonucleotide comprises the sequence

TTCNNNGAA. Claim 1 has been amended to replace "modulating" with "inhibiting" the function of a transcription factor; Applicants note that the Examiner indicated in the Office Action that the specification enables "decreasing the function of a transcription factor . . .." Accordingly, in view of the above, Applicants respectfully assert that the claims are enabled and find adequate written description in the subject specification. Reconsideration and withdrawal of the rejections under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-3 and 7 are rejected under 35 USC §102(b) as anticipated by Liu *et al.* (1997). In addition, claims 1-3 and 7 are rejected under 35 USC §102(a) as anticipated by Boccaccio *et al.* (1998). Claim 8 is rejected under 35 USC §103(a) as obvious over Liu *et al.* (1997) or Boccaccio *et al.* (1998) in view of Bard *et al.* (U.S. Patent No. 6,448,011). As a point of clarification, in regard to the Liu *et al.* reference, which appears to have been published in August of 1997, Applicants respectfully submit that the cited reference is not prior art to the subject application under §102(b) since the cited abstract was not published more than one year before the priority date of the subject application (July 30, 1998). In order to have been prior art under 35 USC §102(b), the Liu *et al.* reference would have to have been published before July 30, 1997.

Under all of the prior art rejections, the Examiner asserts that the Liu *et al.* reference is relied upon as teaching administration of a STAT 5 decoy to Dami/HEL and Meg-01 factor-independent leukemic cell lines and downregulation of the JAK2/STAT5 signaling transduction pathway. The Examiner indicates that the Boccaccio *et al.* reference teaches making an h-SIE decoy of the sequence which binds STAT and administration to MDCK, GTL 16, and MLP29 epithelial cell cultures for inhibition of the STAT transcription factor functions and decreasing growth of epithelial tubules. In the rejection under 35 USC §103, the primary references are relied upon as in the §102 rejection and the Bard *et al.* patent is cited as teaching "pharmaceutically acceptable carriers." Applicants respectfully traverse these rejections.

Applicants respectfully assert that the claimed invention is not anticipated by or obvious over the cited references. However, in a sincere effort to expedite prosecution of the subject application to completion, Applicants have amended the independent claims, as noted above, to include the oligonucleotide sequence limitation of claim 13, *i.e.*, TTCNNNGAA. Applicants note that the

Examiner has indicated in the outstanding Action that claim 13 is free of the prior art. Thus, all of the independent claims, as amended, and the claims dependent therefrom, are free of the prior art.

Accordingly, reconsideration and withdrawal of the rejections under 35 USC §§102 and 103 is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
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DRP/sl
Attachments: New pages 1-3 (Sequence Listing) of the subject specification; Sequence Listing in computer readable format; Supplemental Information Disclosure Statement.

OIPE IAP64 APR 11 2006 PATENT & TRADEMARK OFFICE

SEQUENCE LISTING

<110> Zuckerman, Kenneth S.
Liu, Richard Y.

<120> Method for the Inhibition of Function of STAT Transcription Factors

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OIPE IAP64
APR 11 2006
PATENT & TRADEMARK OFFICE

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on September 8, 2003.

Doran R. Pace, Patent Attorney

SUPPLEMENTAL AMENDMENT UNDER 37 CFR §1.111
Examining Group 1635
Patent Application
Docket No. USF-T176X
Serial No. 09/744,875

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Mary M. Schmidt
Art Unit	:	1635
Applicants	:	Kenneth S. Zuckerman, Richard Y. Liu
Serial No.	:	09/744,875
Filed	:	January 29, 2001
Conf. No.	:	8728
For	:	Method for the Inhibition of Function of STAT Transcription Factors

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

SUPPLEMENTAL AMENDMENT UNDER 37 CFR §1.111

Sir:

An Amendment Under 37 CFR §1.111 was transmitted to the Patent Office on September 3, 2003 in the above-identified patent application. It is respectfully requested that the subject application be amended as follows:

In the Specification

Please substitute the following paragraph beginning on page 6, line 20, through to page 7, line 10:

As shown in the Examples, the applicants have discovered that growth factor independent leukemia cells have a constitutively activated STAT-like DNA-binding factor (DBF). The STAT-like DBF was found to be STAT5. It was also discovered that constitutive activation of STAT5 correlates with cell proliferation. Furthermore the applicants found that cell proliferation could be inhibited by blocking STAT5 transcription factor using a double-stranded oligonucleotide containing the STAT5 binding sequence AGATTTCTAGGAATTCAAATC **(SEQ ID NO:1)** or GCCTGATTTCCCCGAAATGACGGCA **(SEQ ID NO:2)** or GTATTTCCCAGAAAAGGAAC **(SEQ ID NO:3)**, which contain the STAT5 consensus binding site TTCNNNGAA, in which "N" means any nucleotide. This oligonucleotide with the STAT5 binding sequence penetrates into cells and serves as a competitive inhibitor that binds to activated STAT5 in the cells. Oligonucleotide bound, activated STAT5 is not available to bind to endogenous DNA at STAT5 binding sites and therefore ~~can not function i.e.~~ cannot function, *i.e.*, activate the transcription of various cellular genes. Inhibiting the synthesis of protein by this method can have many effects on cells. In the current invention the inhibition of STAT5 function in this manner, prevented cell proliferation and led to the death of human leukemic cells *in vitro*. Hence, the data is highly predictive of the present invention being effective against human malignant cells.

Please substitute the following paragraph beginning on page 20, line 10, through to page 21, line 8:

Preparation of nuclear extracts and gel mobility shift assays were performed according to methods described previously (Yu 1993 Mol Cell Biol 13:2011). Briefly, equal amounts of nuclear proteins (5-10 μg) for each sample were incubated for 30 minutes at 30°C with 10,000 dpm of [^{32}P]-labeled double-strand DNA fragment (IRF-1 GAS), which contains the interferon-γ activation site (GAS) that binds to interferon regulatory factor (IRF-1) (5'-GCCTGATTTCCCCGAAATGACGGCA) **SEQ ID NO 2** (GORODETSKY 1988 GENE 66:87), which

contains an identical sequence to that of Bovine mammary gland factor element (MGFe), TTCCCCGAA **SEQ ID NO 6.** For competition assays, unlabeled FIRE, (5'-AGCGCCTCCCCGGCCGGGGAG) **SEQ ID NO 7,** interferon-stimulated response element (ISG15 ISRE; 5'-GATCGGGAAAGGGAAACCGAAACTGAAGCC) **SEQ ID NO 8,** and sis-inducible element (SIE, 5'-AGCTTCATTTCCCGTAAATCCCTAAGC) **SEQ ID NO 9** also were used as potential DNA-protein binding competitors, by adding 50X molar excess of each unlabeled DNA fragment, along with the [^{32}P]-labeled IRF-1 GAS **(SEQ ID NO. 2)** oligonucleotide probe. Unlabeled MGFe **(SEQ ID NO. 1)** was used as a specific competitor for STAT5 binding to IRF-1 GAS **(SEQ ID NO. 2)**. For gel mobility supershift assays, nuclear extracts were co-incubated with the indicated specific anti-STAT antibodies and the [^{32}P]-labeled oligonucleotide probes. The DNA-protein complexes and unbound probe were separated electrophoretically on 5% native polyacrylamide gels in 0.5 X TBE buffer (44.5 mM Tris, pH 8.0, 1 mM EDTA and 44.5 mM boric acid) for 3 hours at constant 140 volts. The gels were fixed and dried, and the DNA-protein complexes were visualized by autoradiography at ~~-70?C~~ -70°C with Kodak X-OMAT film and a DuPont Cranex lightning-plus intensifying screen.

Please substitute the following paragraph beginning on page 23, line 9:

Applicants analyzed STAT DNA-binding factor activation by gel electrophoretic mobility shift assays (EMSA) with a [^{32}P]-labeled oligonucleotide containing the IRF-1 GAS **(SEQ ID NO. 2)** consensus STAT binding site, as the probe. DNA-binding protein(s) were detected in the nuclear extracts from Dami/HEL and Meg-01 cells in the absence of cytokine exposure (Fig. 2). Addition of as much as 400 ng/ml of TPO or 40 ng/ml IL-3 does not have any further effect on the constitutive DNA-binding protein activity in these growth factor-independent cell lines (Fig. 2). Exposure of these cells to GM-CSF, IL-6, EPO or TNF-α also did not result in significant enhancing or inhibitory effects on the constitutive DNA-binding factor activity. In contrast, no STAT-like DNA-binding factor was detectable in untreated control cells.

Please substitute the following paragraph beginning on page 23, line 27, through to page 24, line 18:

Experiments were performed to identify the specific STAT protein activated in these megakaryocytic leukemic cell lines. First, using a set of oligonucleotides to attempt to inhibit competitively the binding of the STAT-like factor to [^{32}P]-labeled IRF-1 GAS **(SEQ ID NO. 2)**. When Dami/HEL and Meg-01 nuclear extracts were co-incubated with the labeled MGFe probe **(SEQ ID NO. 1)** plus a 100-fold molar excess of unlabeled SIE **(SEQ ID NO. 9)** or IRF-1 GAS **(SEQ ID NO. 2)** (Fig 4) or FIRE **(SEQ ID NO. 7)** or ISRE **(SEQ ID NO. 8)** oligonucleotides, which do not contain TTCCCCGAA sequence, no competitive inhibition of the formation of DNA-protein complexes was observed. However, a 50-fold molar excess of the unlabeled MGFe **(SEQ ID NO. 1)**, which contains the same TTCCCCGAA STAT-binding sequence as IRF-1 GAS **(SEQ ID NO. 2)**, completely abolished the formation of the labeled DNA-protein complexes. Similar results were found with Meg-01.

When the nuclear extracts from TPO-treated Mo7e cells were incubated with [^{32} P]-labeled IRF-1 GAS **(SEQ ID NO. 2)** probe or the [^{32}P]-labeled probe plus a 50-fold molar excess of unlabeled FIRE **(SEQ ID NO. 7)**, ISRE **(SEQ ID NO. 8)**, SIE **(SEQ ID NO. 9)** or MGFe **(SEQ ID NO. 1)** oligonucleotides, the cytokine-induced DNA-binding factor in Mo7e cells had the same features as the constitutively activated STAT-like factor in Dami/HEL cells. Both of the factors are able to bind to the IRF-1 GAS **(SEQ ID NO. 2)** probe, and their binding activity could be abolished completely by unlabeled MGFe **(SEQ ID NO. 1)**, but not by oligonucleotides that do not contain the TTCNNNGAA sequence.

Remarks

An Amendment Under 37 CFR §1.111 was transmitted to the Patent Office on September 3, 2003 in the subject application. Following the September 3 Amendment, claims 1, 8-13, 15, 16, and 19-57 are pending in the subject application and currently before the Examiner for consideration. By this Supplemental Amendment, Applicants have amended the subject specification at pages 6, 7, 20, 21, 23, and 24 to include the SEQ ID numbers for oligonucleotides of the invention and to correct minor typographical errors. Applicants respectfully submit that these amendments will require no further search or examination on the part of the Examiner and do not constitute new matter. Entry and consideration of the amendments presented herein is respectfully requested. Favorable consideration of the pending claims is respectfully requested.

In view of the foregoing remarks and amendments to the specification, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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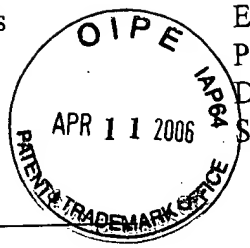
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on October 29, 2004.

Doran R. Pace, Patent Attorney



AMENDMENT UNDER 37 CFR §1.111
Examining Group 1635
Patent Application
Docket No. USF-T176X
Serial No. 09/744,875

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Sean R. McGarry
Art Unit	:	1635
Applicants	:	Kenneth S. Zuckerman, Richard Y. Liu
Serial No.	:	09/744,875
Filed	:	January 29, 2001
Conf. No.	:	8728
For	:	Method for the Inhibition of Function of STAT Transcription Factors

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 CFR §1.111

Sir:

In response to the Office Action dated July 29, 2004, please amend the above-identified patent application as follows:

In the Claims

1 (currently amended). A method for inhibiting the function of a transcription factor, said method comprising administering an effective amount of a double-stranded oligonucleotide, said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1), and wherein said transcription factor binds to said oligonucleotide.

2-7 (canceled).

8 (currently amended). A composition for inhibiting a transcription factor in a cell, said composition comprising a double-stranded oligonucleotide, said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1), and wherein said transcription factor binds to said oligonucleotide.

9 (previously presented). The composition according to claim 8, wherein said transcription factor is activated.

10 (previously presented). The composition according to claim 9, wherein said transcription factor is constitutively activated.

11 (previously presented). The composition according to claim 8, wherein the cell is a malignant cell.

12 (previously presented). The composition according to claim 8, wherein the cell is a leukemia cell.

13 (previously presented). The composition according to claim 8, wherein said transcription factor is STAT5.

14-15 (canceled).

16 (currently amended). A method of inhibiting proliferation of a tumor cell by administering an effective amount of a double-stranded oligonucleotide, said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1), and wherein a transcription factor in said tumor cell binds to said oligonucleotide, the transcription factor activity being correlated to proliferation of said tumor cell.

17-18 (canceled).

19 (currently amended). A method of ~~removing~~ killing a tumor cell in vitro by exposing a cell culture to an effective amount of a double-stranded oligonucleotide, said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1), and wherein a transcription factor in said tumor cell binds to said oligonucleotide, the transcription factor activity being correlated to proliferation of said tumor cell.

20 (currently amended). An agent comprising ~~an effective amount of~~ a double-stranded oligonucleotide ~~of claim 8~~, said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1) and a pharmaceutically ~~effective~~ acceptable carrier, diluent, or adjuvant.

21 (previously presented). The agent according to claim 20, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1).

22 (previously presented). The agent according to claim 20, wherein said transcription factor is STAT5.

23 (previously presented). The agent according to claim 20, wherein said transcription factor is activated.

24 (previously presented). The agent according to claim 23, wherein said transcription factor is constitutively activated.

25 (previously presented). The agent according to claim 20, wherein said cell is a malignant cell.

26 (previously presented). The agent according to claim 20, wherein said cell is a leukemia cell.

27 (previously presented). The agent according to claim 20, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

28 (previously presented). The agent according to claim 20, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

29 (previously presented). The agent according to claim 20, wherein said cell is a human cell.

30 (previously presented). The method according to claim 1, wherein said transcription factor is STAT5.

31 (canceled).

32 (previously presented). The method according to claim 1, wherein said transcription factor is activated.

33 (previously presented). The method according to claim 32, wherein said transcription factor is constitutively activated.

34 (previously presented). The method according to claim 1, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

35 (previously presented). The method according to claim 1, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

36 (canceled).

37 (previously presented). The composition according to claim 8, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

38 (previously presented). The composition according to claim 8, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

39 (previously presented). The composition according to claim 8, wherein said cell is a human cell.

40 (canceled).

41 (previously presented). The method according to claim 16, wherein said transcription factor is STAT5.

42 (previously presented). The method according to claim 16, wherein said transcription factor is activated.

43 (previously presented). The method according to claim 42, wherein said transcription factor is constitutively activated.

44 (previously presented). The method according to claim 16, wherein said cell is a malignant cell.

45 (previously presented). The method according to claim 16, wherein said cell is a leukemia cell.

46 (previously presented). The method according to claim 16, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

47 (previously presented). The method according to claim 16, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

48 (previously presented). The method according to claim 16, wherein said cell is a human cell.

49 (canceled).

50 (previously presented). The method according to claim 19, wherein said transcription factor is STAT5.

51 (previously presented). The method according to claim 19, wherein said transcription factor is activated.

52 (previously presented). The method according to claim 51, wherein said transcription factor is constitutively activated.

53 (previously presented). The method according to claim 19, wherein said cell is a malignant cell.

54 (previously presented). The method according to claim 19, wherein said cell is a leukemia cell.

55 (previously presented). The method according to claim 19, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

56 (previously presented). The method according to claim 19, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

57 (previously presented). The method according to claim 19, wherein said cell is a human cell.

58 (new). The method according to claim 1, wherein said transcription factor is present in a cell.

59 (new). The method according to claim 58, wherein said cell is a human cell.

60 (new). The method according to claim 58, wherein said cell is a malignant cell.

61 (new). The method according to claim 58, wherein said cell is a cancer cell.

62 (new). The method according to claim 16, wherein said cell is a cancer cell.

63 (new). The method according to claim 19, wherein said cell is a cancer cell.

64 (new). The composition according to claim 8, wherein said oligonucleotide consists of the nucleotide sequence 5'-AGATTTCTAGGAATTCAAATC-3' (SEQ ID NO: 1).

65 (new). The agent according to claim 20, wherein said oligonucleotide consists of the nucleotide sequence 5'-AGATTTCTAGGAATTCAAATC-3' (SEQ ID NO: 1).

66 (new). The method according to claim 1, wherein said oligonucleotide consists of the nucleotide sequence 5'-AGATTTCTAGGAATTCAAATC-3' (SEQ ID NO: 1).

67 (new). The method according to claim 16, wherein said oligonucleotide consists of the nucleotide sequence 5'-AGATTTCTAGGAATTCAAATC-3' (SEQ ID NO: 1).

68 (new). The method according to claim 19, wherein said oligonucleotide consists of the nucleotide sequence 5'-AGATTTCTAGGAATTCAAATC-3' (SEQ ID NO: 1).

69 (new). A method for treating a person or animal having a disorder associated with the activation of a transcription factor, said method comprising administering to said person or animal an effective amount of a composition comprising a double-stranded oligonucleotide, said oligonucleotide having a nucleotide sequence comprising the sequence TTCNNNGAA, wherein N represents any nucleotide, wherein said oligonucleotide comprises the sequence AGATTTCTAGGAATTCAAATC (SEQ ID NO:1), wherein said transcription factor binds to said oligonucleotide.

70 (new). The method according to claim 69, wherein said transcription factor is STAT5.

71 (new). The method according to claim 69, wherein said transcription factor is activated.

72 (new). The method according to claim 71, wherein said transcription factor is constitutively activated.

73 (new). The method according to claim 69, wherein said oligonucleotide comprises multiple copies of said nucleotide sequence TTCNNNGAA.

74 (new). The method according to claim 69, wherein said oligonucleotide comprises two copies of said nucleotide sequence TTCNNNGAA.

75 (new). The method according to claim 69, wherein said disorder is a neoplasm.

76 (new). The method according to claim 75, wherein said neoplasm is a leukemia or carcinoma.

77 (new). The method according to claim 69, wherein said composition further comprises a pharmaceutically acceptable carrier, diluent, or adjuvant.

Remarks

Claims 1, 8-13, 15, 16, and 19-57 are pending in the subject application. Applicants acknowledge that claims 1, 16, 19, 30-35, and 40-57 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have canceled claims 15, 31, 36, 40, and 49, amended claims 1, 8, 16, 19, and 20, and added new claims 58-77. Support for the amendments and new claims can be found throughout the subject specification. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1, 8-13, 16, 19-30, 32-25, 37-39, 41-48, and 50-77 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants gratefully acknowledge the Examiner's indication that claim 15 is objected to but would be allowable if rewritten into independent form to include the limitations of any base and intervening claims.

Claims 20-29 are rejected under 35 USC §112, second paragraph, as indefinite. The Examiner asserts that the term "an effective amount" of a double-stranded oligonucleotide in claim 20 renders the claim indefinite. The Examiner also asserts that the term "pharmaceutically effective carrier" renders claim 20 indefinite. Applicants have amended claim 20 to delete reference to the term "an effective amount." Applicants have also amended claim 20 to recite a "pharmaceutically acceptable carrier, diluent, or adjuvant." Support for the amendment can be found, for example, at page 10, lines 6-7, of the subject specification. Applicants respectfully assert that the term does not render the claims indefinite. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 8-13 and 37-39 are rejected under 35 USC §102(b) as anticipated by either of Pearse *et al.* (1993) or Wegenka *et al.* (1993). In addition, claims 20 and 22-29 are rejected under 35 USC §102(b) as anticipated by or, in the alternative, under 35 USC §103(a) as obvious over either of Pearse *et al.* (1993) and Wegenka *et al.* (1993) taken separately. The Examiner indicates that the Pearse *et al.* and Wegenka *et al.* (1993) references disclose a composition containing double-stranded oligonucleotides that comprise the consensus nucleotide sequence recited in the claims. Applicants respectfully traverse these grounds of rejection.

Applicants respectfully assert that neither of the cited references teach or suggest Applicants' claimed invention. The cited references do not teach or suggest anything regarding use of the oligonucleotides disclosed therein in methods to inhibit transcription factor activity or to inhibit tumor cell proliferation. However, by this Amendment, Applicants have amended independent composition claims 8 and 20 to recite the sequence of the oligonucleotide (SEQ ID NO: 1) of claim 15 indicated as allowable by the Examiner. These amendments have been made solely to expedite prosecution of the subject application. Applicants have also amended independent method claims 1, 16, and 19 to recite that the oligonucleotide used in the claimed methods has the sequence of SEQ ID NO: 1. Applicants respectfully request rejoinder (under MPEP §821.04) of claims 1, 16, 19, 30-35, and 40-77 in the subject application upon an indication of allowance of the composition claims in the subject application. In view of the amendments to recite that the oligonucleotide comprises SEQ ID NO: 1 in all the pending claims, Applicants respectfully assert that the rejections over the cited references are moot. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §§102 and 103 is respectfully requested.

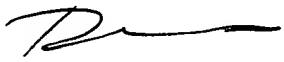
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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